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(57) Abstract

This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising a pharmaceutical grad viscoelastic fraction selected form a group consiting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, and hydroxypropylmethylcellulose. In particular these solutions have a surface tension of between 40 and 65 dynes/cm^2; particularly a viscoelastic fraction has an average molecular weight of at least 50,000. In some embodiments a physiological buffer fraction is present. This invention further encompasses a method of using the claimed composition.

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SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

This application is a continuation-in-part of copending U.S. Pat. App. 08/061,773 filed May 13, 1993, which is a continuation of U.S. Pat. App. 07/440,078 filed November 22, 1989, now abandoned.

Field of the Invention.

The present invention relates to ophthalmic solutions for use during ocular and intraocular surgery, and more particularly to the use of surface active viscoelastic solutions during the extraction of a cataractous human lens and the implantation of a prosthetic ocular and intraocular lens. During surgery, the use of ophthalmic infusions with controlled physical properties, especially surface activity and viscoelastic properties, is advantageous for (1) replacing the fluid aqueous humor or ocular and intraocular air, (2) protecting the internal structures of the eye from accidental instrument or ocular and intraocular prosthetic device contact, (3) preventing irrigation damage by solutions used in routine cataract surgery, and (4) retarding aspiration from the eye of the viscoelastic solution during the surgical procedure. In addition, the invention relates to a method of adhering a contact lens to the surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. In

another application, the viscoelastic solution of this invention is used by injecting the solution into or under tissues within the eye, such as to dissect tissue off of the retina.

Background of the Invention

In the past, biocompatible polymers used in ocular and intraocular surgery have been the naturally occurring mucopolysaccharides hyaluronic acid and chondroitin sulfate; mixtures of hyaluronic acid and chondroitin sulfate; and, cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC). Table 1 presents data reported in Viscoelastic Materials, Ed. E.S. Rosen, Proceedings of the Second International Symposium of the Northern Eye Institute, Manchester [U.K.], 17-19 July, 1986 (Pergamon Press, New York) as to the molecular weight of commercially available ocular products. Depending on the source from which these mucopolysaccharides are drawn, the molecular weights are estimated in the 50,000 range with the hyaluronic acid extending upwards to the 8×10^6 range. Hyaluronic acid was first isolated and characterized by Meyer, Palmer and reported in the J. Biol. Chem., Vol. 107, p. 629 (1934) and Vol. 114, p.689 (1936) and by Balazs in the Fed. Proc. Vol. 17, p. 1086 (1958); and chondroitin sulfate by Bray et al. in Biochem. J. Vol. 38, p. 144 (1944); and Patat, Elias, Z. Physiol. Chem. vol. 316, p. 1 (1959).

Literature in the art describes the basic isolation and characterization of the viscoelastic solutions. It is a surprising feature of this invention which describes the control

of viscoelastic properties as related to the surface activity, or the solution fracturing under applied stress. In particular, it is surprising to manipulate or enhance the physical properties of viscoelastic solutions of mucopolysaccharides, hyaluronic acid, and/or chondroitin sulfate. It is believed that disclosure here of a processes to provide hyaluronic acid and species thereof with controlled surface activity is unique. This is also especially true of the control of surface activity of mucopolysaccharide solutions by the addition of biologically compatible surfactants. A characteristic feature of biologically compatible surfactants is the absence of observed alteration in cellular physiology upon contact. Early work in the viscoelastic field was presented by the inventor of this disclosure and his associates. Benedetto, D.A. et. al., Viscoelastic Materials: Basic Science and Clinical Application, (Symposium Proceedings), University of Manchester, England, July 17-19, 1986.

As to commercial production, a review of the ophthalmic pharmacopoeia reveals there are several viscoelastic solutions produced for ocular and intraocular use during ophthalmic surgery. The most common application for these solutions is in the intraocular lens implant procedure for human cataract surgery. This procedure involves extraction of the cataractous human lens through a small surgical opening in the eye and the replacement of the lens by a prosthetic intraocular lens placed in situ. Biocompatible polymers presently or previously in use are hyaluronic acid (Healon™, Amvisc™); chondroitin sulfate, and

a combined solution of hyaluronic acid and chondroitin sulfate (Viscoat™); and a hydroxypropylmethylcellulose solution (Occucoat™). Research conducted recently demonstrates that Healon™ and Amvisc™ are not surface active, but Viscoat™ and Occucoat™ are.

Chondroitin sulfate does not exist as a free polysaccharide in its native state, but as a proteoglycan. It is obtained from sources associated with protein contaminants. The avoidance of chondroitin sulfate avoids a potential source of pyrogenic reaction, and the substantial cost associated with protein removal.

Summary of the Invention

The invention presented herein discloses modified mucopolysaccharide or viscoelastic solutions for use as biologically active therapeutic infusions. In one form of the invention, the mucopolysaccharide solution is formed from a viscoelastic fraction and a buffer fraction. It has been found that when a new synthetic molecule acyl-substituted hyaluronic acid is employed as the viscoelastic fraction, control of surface activity is achieved. An indicia of this is the decrease of the surface tension of the solution which is now within predetermined limits discussed below. Surface tension modification is also accomplished with viscoelastic fractions in which the acyl-substituted hyaluronic acid is mixed with one or more of hyaluronic acid; and hydroxypropylmethylcellulose. In certain applications, the viscoelastic solution of this invention is used in a method of adhering a contact lens to the

surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. This is particularly useful in facilitating surgical procedures. In another application, the viscoelastic solution of this invention is used by injection the solution into or under structures or tissues within the eye, such as to dissect tissue off of the retina.

In the broadest terms, surface active viscoelastic solutions with controlled solution properties, are characterized by surface tension, equilibrium contact angle, dynamic viscosity, and cohesiveness (the measure of solution fracture under stress). In a particular embodiment, this invention is delimited by the three dimensional representation of Fig. 7.

In one example, bioengineered hyaluronic acid from a bacterial source with an average molecular weight of 50,000 is modified by acyl substitution with three to twenty carbon atom acyl groups so that the resultant surface tension of such a solution is between 40 and 65 dynes/cm^2. In the practice of this invention, a viscoelastic solution having a surface tension of less than about 56 dynes/cm^2, and more particularly, less than about 50 dynes/cm^2 is of particular advantage.

This invention comprises a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

optionally with a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C; and,

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2; and further,

optionally wherein the solution has an osmolality of from about 250 to about 400 milliosmoles, or is generally isotonic with ophthalmic tissue.

In some embodiments the modified mucopolysaccharide solution viscoelastic fraction has an average molecular weight of at least 50,000. Reference is further made to the viscoelastic fraction being an acyl-substitute hyaluronic acid having acyl groups thereof with three to twenty carbon atoms.

In particular applications the modified mucopolysaccharide solution of this invention includes a surfactant fraction of a biocompatible component selected from a group consisting of

phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, with the surfactant present in an amount sufficient to produce the required surface tension. In particular, a biological surfactant fraction of a free fatty acid is present in an amount of less than 1 mg/ml. Further embodiments include a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml. In a preferred embodiment the surfactant fraction of biocompatible component is a free fatty acid.

In a further embodiment the modified mucopolysaccharide solution has a viscoelastic fraction of a mixture of acyl-substituted hyaluronic acid and hyaluronic acid, and particularly with a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, with surfactant present in an amount sufficient to produce the required surface tension, usefully in an amount less than 10 micrograms/ml. Preferred surfactants are free fatty acids such as oleic acid.

Particular modified mucopolysaccharide solutions of the invention are characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution

is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

In another embodiment this present invention comprises a modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml; and,

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2.

In some embodiment of this modified mucopolysaccharide solution a particular polymeric fraction is hyaluronic acid.

Particular modified mucopolysaccharide solutions of the invention are characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured, which optionally include those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0.

Another embodiment of the present invention includes a pharmaceutically acceptable modified mucopolysaccharide solution (particularly a surface active mucopolysaccharide) absent chondroitin sulfate having a surface tension of between 40 and 65 dynes/cm^2; and,

a viscosity of between 10,000 and 100,000 centipoise (particularly an average molecular weight of at least 50,000) when measured at a shear rate of 3 sec^{-1} at 25 C.

optionally wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2, and further a surface tension of less than about 50 dynes/cm^2.

In this embodiment of a modified mucopolysaccharide solution a particular polymeric fraction is hyaluronic acid.

In certain applications the mucopolysaccharide solution further comprises a biological surfactant selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants.

Yet a further embodiment of the invention includes a method of protecting internal ocular structures during ocular surgery and retarding aspiration of material from the ocular surgery site by the steps of:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction with a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C. In such embodiment a

preferred method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2. In certain embodiments a "sloped" syringe absent sharp reductions in cross sectional area is useful.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

An additional embodiment of the invention includes a method of protecting internal ocular structures during ocular surgery by providing a viscoelastic solution that coats ocular structures at a surgical site such that aspiration of the viscoelastic solution is retarded, said method being:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution absent chondroitin sulfate and having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C. In such embodiment a preferred method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

A next method of the present invention includes a method of protection of internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

intraocularly introducing a modified mucopolysaccharide solution during ophthalmic surgery wherein said solution comprises

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent

chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

In such embodiment a specific method entails intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution by a syringe of about 1.13 cm^2 in cross section or less, and optionally about 0.57 cm^2 or less, and further optionally about 0.16 cm^2.

Further in this method the invention includes particular modified mucopolysaccharide solutions characterized by aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and particularly in a range of 50 to 200 mm Hg, wherein the solution is easily fractured. Similarly, those solutions with an aspiration profile of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred.

A next embodiment of the invention comprises a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2 (particularly less than about 56 and more particularly less than about 50 dynes/cm^2); and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from a group consisting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, chondroitin sulfate C, and hydroxypropylmethylcellulose, said fraction with a surface tension of between 40 and 65 dynes/cm^2; particularly a viscoelastic fraction has an average molecular weight of at least 50,000; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

whereby, upon infusion of modified mucopolysaccharide solution at the site, the surface activity of the solution enhances coating of the site.

A specific modified mucopolysaccharide solution is one with an acyl-substituted hyaluronic acid, and a preferred viscosity is between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C, and optionally further including a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in a trace amount sufficient to produce said surface tension. In one embodiment the surfactant is present in an amount less than 10 micrograms/ml. A preferred surfactant is oleic acid. A preferred modified mucopolysaccharide solution comprises a mixture of an acyl-substituted hyaluronic acid and hyaluronic acid.

In a particular application this invention includes a modified mucopolysaccharide solution for use a biologically compatible therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from a group consisting of hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, and chondroitin sulfate C, said fraction having an average molecular weight of at least 50,000.

a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in a trace amount sufficient to produce a surface tension of between 40 and 65 dynes/cm^2; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

whereby, upon infusion of modified mucopolysaccharide solution at the site, the surface activity of the solution enhances coating of the site and results in retardation of aspiration at the site. A preferred modified mucopolysaccharide solution has a viscoelastic fraction of hyaluronic acid, and, optionally, a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1}, and further optionally, a surfactant, particularly oleic acid, and particularly with surfactant present in an amount less than 10 micrograms/ml.

In one embodiment this invention includes a modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures comprising:

an optically clear polymeric fraction of high-purity mucopolysaccharides and mixtures thereof, said polymeric fraction selected from the group consisting of hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B, chondroitin

sulfate C, and mixtures of hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B and chondroitin sulfate C with an average molecular weight of at least 50,000;

a biological surfactant fraction of a free fatty acid present in an amount of less than 1 mg/ml; and,

optionally a physiological buffer fraction, such that the viscoelastic comprises about a 0.1% percent of the solution to about 5% of the solution, by weight, and preferably from about 0.5 % to about 3%;

whereby, upon the modified mucopolysaccharide solution being placed in the eye space during surgery, the surgeon can observe the ocular and intraocular structure through the optically clear solution, and the corneal endothelium is protected from accidental touch by surgical instruments, ocular and intraocular prosthetic devices, and in ocular and intraocular irrigating solutions, particularly wherein the polymeric fraction is hyaluronic acid, and particularly wherein the solution has a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

An additional embodiment of this invention is a method of adhering a contact lens to the surface of the eye in operational-optical connection with said eye, by the step of interposing between said lens and said eye surface an adhering amount of substantially transparent modified mucopolysaccharide solution of this invention. In the practice of this method, an apparatus comprising a contact lens and a layer of transparent modified mucopolysaccharide solution is employed. Preferably the optical properties of such lens/solution unit will be

configured to facilitate observation of internal ophthalmic structures when the observer is positioned to peer directly through the lens. Alternatively, the "observer" may be a television, film or other camera directed into the lens. Further, the camera lens may substitute for the contact lens, and thus with a layer of the mucopolysaccharide solution of this invention, be in direct contact with the eye.

A yet further embodiment of this invention is a method of hydraulically positioning intra-optic structures or tissues by the step of applying against such tissues under elevated hydrostatic pressure the modified mucopolysaccharide solution of this invention. Typically this would be applied to dissect or elevate hyperplastic tissue that grows over the retina in certain pathologies. The degree of elevation of hydrostatic pressure would be that sufficient to move the intended tissue.

An additional aspect of this invention is based upon ophthalmic osmolality. Osmolality of from about 250 milliosmoles to about 400 milliosmoles is essentially isotonic to optic structures. Lower osmolality will cause optic structures to swell and higher osmolality will cause shrinkage.

Brief Description of the Drawings

Fig. 1 is a plot of Kc/R_θ against concentration, C. The material tested is high molecular weight HA. The molecular weight was obtained from the inverse of the abscissa extrapolated to zero concentration.

Fig. 2 is a plot of maximum load versus time for high molecular weight HA. The maximum load was determined as the largest load needed to force a sample of viscoelastic from a syringe through a 23 gauge needle.

Fig. 3. is a graphic comparison of the surface tension of one embodiment of of a solution of the present invention as compared to the surface tension of a commercially available HPMC ocular solution, and a commercially available HA ocular solution.

Fig. 4 is a graphic comparison of the viscosity of one embodiment of a solution of the present invention as compared with other, commercially available, ocular solutions, and measured at a shear rate of 0.35 sec^{-1}. Standard deviation is shown in gray, and the average values in black. All columns except E and F are statistically different than B, Healon™

Fig. 5 is a plot comparison of the aspiration characteristics of the *in situ* retention of solutions embodying the present invention as compared other viscoelastic ocular solutions.

Fig. 5(a) repeats Fig. 5 with a preferred range shaded.

Fig. 6 is a plot of viscosity against surface tension enclosing a preferred range for solutions of the present invention.

Fig. 7 is a three dimensional plot of viscosity against surface tension against "aspiration profile" (the slope of the % of aspiration between 50 mmHg and 90 mmHg under test conditions as plotted in Fig. 5, and excluding sigmoidal curves) enclosing in cubic representation a of viscoelastic solutions of the present invention.

Fig. 8 is a graphic representation of stress (MPa) recorded by injecting various solutions of varying viscosity from a syringe and through a 23 gauge needle.

Fig. 9(a), (b), and (c) represent various embodiments of "sloped" syringe absent sharp reductions in cross sectional area.

Fig. 10(a) and (b) are diagrammatic representations of various embodiments of an apparatus for viewing the interior of the eye (depicted in contact with an eye).

Detailed Description of the Invention

In general terms, viscoelastic solutions are placed in the anterior chamber of the eye during ocular and intraocular lens implant surgery, replacing the fluid aqueous humor of the eye. Clearly, hosts suitable for application of the present materials and methods are ocular and intraocular site of animal requiring

such material. In particular, host sites are mammalian eyes, particularly those of humans, and most particularly the anterior chamber thereof. By nature of their viscosity (10,000 to 1 million times greater than that of aqueous humor), viscoelastic solutions allow the eye to maintain its normal shape and ocular and intraocular structural relationships during cataract extraction and lens implantation. When the fluid aqueous humor leaks from the eye, as when the eye is opened by incision at the time of surgery, the anterior structures of the eye collapse. There is no space within the anterior segment of the eye within which the surgeon can place instruments for cataract extraction without damaging ocular and intraocular structures by touch from his instruments. Air may be used to maintain this space, but it is more likely to leak from the eye compared to a viscous solution. In addition, air on top of other ocular fluids, does not allow the surgeon to visualize ocular and intraocular structures, as effectively as through clear viscoelastic solution. Viscoelastic solutions are fluids which resist flow by nature of their high viscosity. These fluids are elastic because they have a "memory." They return to approximately their original shape after stretch. These solutions are optically clear and are basically aqueous solutions of higher molecular weight polymers in the molecular weight range of 50,000 to 8 million.

As used herein, in reference to HPMC, the term "low" in reference to "low molecular weight" HPMC, "HPMC(L)," shall mean below about 250,000 MW and particularly below about 150,000 MW, while "high" molecular weight HPMC, "HPMC(H)," shall mean above

about 250,000 MW and particularly above about 300,000 MW. In reference to HA, the term "low" in reference to "low molecular weight" HA, "HA(L)," shall mean below about 1,500,000 MW, and particularly below about 700,000 MW, while "high" molecular weight HA, "HA(H)," shall mean above about 1,500,000 MW, and in particular above about 3,000,000 MW, and more particularly above about 5,000,000 MW.

In addition to being viscous and elastic, a mild degree of surface activity is a desirable property of viscoelastic solutions. Surface activity is a measure of the ability of a solution to coat or spread on a surface. Solutions which coat the internal structures of the eye are better able to protect the eye from accidental touch by surgical instruments or an intraocular lens. In addition, these solutions protect the eye from irrigation damage by irrigating solutions used in routine cataract surgery. Viscoelastic solutions which are not surface active and do not fracture at aspiration pressures used during cataract surgery are too easily aspirated from the eye during cataract surgery. The surgeon is then faced with lack of protective ophthalmic solution, which necessitates replacement of viscoelastic at additional cost.

Particular note is made of the distinction between viscosity and pseudoplasticity (which includes thixotropy). Viscosity is the propensity of a solution to resist flow. Pseudoplasticity is the general case of a change in viscosity

with applied force, which may or may not be reversible. Thixotropy describes reversible shear thinning, limited largely to the period while subject to shear.

Surface tension is a measure of the tendency of molecules within a solution to attract or repel each other. With high mutual attraction, the solution has a high surface tension and the solution is cohesive. Without being bound by any particular theory, it is believed that at a solution interface (air/liquid, liquid/liquid, liquid/solid)) of a solution of high surface tension, the tendency would be for solution molecules to be drawn back into the solution. In a solution of low surface tension (i.e., a surfactant type solution) solution molecules accumulate at an interface because the molecules are not completely soluble within the bulk solution. It is presumed that the hydrophobic/hydrophillic structure of surfactant molecules cause them to accumulate at a solution interface, representing the lowest energy state.

Particular attention is drawn to the unique confluence of physical characteristics present in the viscoelastic solution of the present invention. Considering viscosity, Fig. 4 discloses that a variety of viscosities (Fig. 4, Examples E-H) may be obtained within the practice of this invention, while still presenting the required surface tension and aspiration profile. Viscosity is presented in m Pa·s or millipascal·seconds. One Pa·s equals 1000 centipoise, and one mPa·s equals 1 centipoise. Fig 4. data was obtained at a shear rate of 0.35 sec^{-1}. The solutions represented are as follows: A is 2% HPMC(L) and a

molecular weight of about 200,000 with a viscosity of 98 cps; B is 2% HPMC with a viscosity of 3680 cps; C is 1% HA(L) (L denotes an average MW of about 0.8×10^6) solution with a viscosity of 424 cps; D is 1% HA(H) (H denotes an average MW of about 2.1×10^6) solution with a viscosity of 21,845 cps; E is a mixture of 2% HPMC(L) and 1% HA(L) with a viscosity of 2,095 cps; F is a mixture of 2% HPMC(L) and 1% HA(H) with a viscosity of 38,460 cps; G is a mixture of 2% HPMC(H) and 1% HA(L) with a viscosity of 25,344 cps; and H is a mixture of 2% HPMC(H) and 1% HA(H) with a viscosity of 56,691 cps. The substantial and synergistic increase in HPMC viscosity in combination with a viscoelastic, such as, HA is noted.

Fig. 3 compares the surface tension of various ocular solutions. Solution A is Occucoat™, a commercially available HPMC solution, measured at 1:10 dilution as having a surface tension of 43.0 ± 1.41 dynes/cm; Solution B is Healon™, a commercially available HA solution, measured at 62.7 ± 6.51 dynes/cm, Solution C, low molecular weight HPMC, and Solution D, high molecular weight HPMC were measured at about 50 ± .75 dynes/cm; Solution E, low molecular weight HA, and Solution F, high molecular weight HA were measured at about 70 ± 2.25 dynes/cm; Solutions G through J are mixtures of 1% HA and 2% HPMC all having a surface tension of about 50 ± 0.58 dynes/cm . Specifically Solution G is HA(L) and HPMC(L). Solution H is HA(H) and HPMC(L). Solution I is HA(L) and HPMC(H). Solution J

is HA(H) and HPMC(H). Note that Fig. 3 solutions A, C, D, G-J exhibit surface tension statistically significantly different than B, Healon™.

Further note is made of the fracture and aspiration characteristics of the mucopolysaccharide solutions of this invention. In ocular surgery, a tiny cannula is used to inject/remove viscoelastic solutions. The claimed solutions easily fracture when vacuum is applied by a cannula. Thus to remove all of such solution, the cannula must be repeatedly moved to remain in contact with the solution. In contrast, a typical solution of high molecular weight as known in the prior art fall into two groupings. One, typified by Healon™, an HA solution will not fracture easily, nor will it elute in solutions typically present during ophthalmic surgery and generally aspirates only in a bolus. The other grouping comprises solutions "incohesive" solutions. "Incohesive" solutions elute so rapidly that, they are removed from the ocular surgical site by irrigation fluids. This rapid elution destroys the viscosity, coating and shock absorbing properties for which they were being used, leaving the field unprotected.

A useful measure of fracture and aspiration characteristics of various solutions is set forth in Fig. 5. In particular, Fig. 5 is a clear representation of the achievement of protective *in situ* retention of a solution embodying the present invention as compared to an HA ocular solution -- independent of viscosity. The aspiration behavior of HA is seen to be generally sigmoidal. At low vacuum. only small amounts of HA

are aspirated, while at vacuums of about 40 mm Hg, almost 100% of the HA is removed. In contrast, a mixture of HA and HPMC, is removed in a manner generally linear to the amount of vacuum applied, permitting gradual removal, which may be continued to almost total removal, but not removal generally as a single bolus. Again, this linear removal profile may be obtained with solutions of a viscosity similar to that of HA alone, and substantially above the viscosity of HPMC alone. Particularly useful viscoelastic solutions are those whose aspiration characteristics are non-sigmoidal under the described experimental conditions, and most particularly those which are generally linear with a slope of between about horizontal and about 1.5, (and preferably between about horizontal and about 1) as presented in Fig. 5 as percentage aspiration against mmHG from about 50 mm HG to about 90 mm HG, using a 23 gauge needle. The procedure is more fully described in Aspiration Profile (below). A preferred range is shaded in Fig. 5(a) which reproduces Fig 5.

Figs. 6 and 7 define meets and bounds of particular embodiments of this invention. Fig. 6 is seen to delimit suitable viscoelastics by viscosity and surface tension. Particularly preferred are those solutions of less than 56 dynes/cm and more particularly, those of less than 50 dynes/cm surface tension. Occucoat™ is plotted as point "I" and Healon™ is plotted as point "II." Fig. 7 graphically distinguishes the chondroitin free viscoelastic solution of the present invention from particular commercial viscoelastic solutions. Three

parameters, viscosity, surface tension, and aspiration profile are presented. It is the three dimensional area circumscribed by these parameters that are particularly useful. More particularly is the circumscribed area, below 56 dynes/cm in surface tension and more particularly still, the circumscribed area below 50 dynes/cm surface tension.

Given the delimiting parameters of the claimed viscoelastic solutions, a general protocol to achieve such solutions is presented. Viscosity is increased or decreased in relation to highest molecular weight viscoelastic material or polymeric material present. If the viscosity of that highest molecular weight material is the viscosity desired, no adjustment is required. If lower viscosity is desired, increased dilution, or substitution of material of identical structure, but lower molecular weight, decreases viscosity. When increasing dilution, attention must be paid to the resulting solution osmolarity. Aspiration characteristics of the invention are modified by admixing viscoelastic polymers with low molecular weight polymers of the same or other species, including polysaccharides such as HPMC. Such additions increase ease of fracture on aspiration. Surface tension is reduced by addition of surfactant or by modification of a non-surface active molecule to be surface active. Particular note is made of the surface activity of HPMC. In the case of HA, surface activity adjustment entails addition of a lipophilic acyl side chain or chains. Osmolality is adjusted by modification of the solute/solvent ratio.

All of the foregoing parameters are most easily adjusted by empirical methods such a a checkerboard type assay, increasing the amount of each particular factor (serial dilution) until the desired characteristic is obtained. However, approximate methods of calculation are possible.

By this disclosure, non-surface active viscoelastic solutions are modified to make them surface active. This can be accomplished by the addition of any one of many biocompatible surfactants, or by substitution or admixture of hyaluronic acid polymer in a viscoelastic solution with hyaluronic acid polymer having a lipophilic side chain. A lipophilic acyl side chain substituted hyaluronic acid renders the previously completely water soluble molecule surface active. Biological surfactants belong to the following categories of chemical substances: phospholipids, monoglycerides, free fatty acids or fatty acid soaps, cholesterol, and pharmaceutical grade nonionic surfactants. Though it is understood that HPMC has some surfactant activity, as used herein, biological surfactants excludes HPMC. Preliminary results with oleic acid, a fatty acid component of phospholipids which composes most mammalian cell membranes, indicate that at a concentration of 1 microgram oleic acid per ml of solution can provide moderate surface activity to a solution which was not previously surface active. During routine cataract surgery, particular claimed viscoelastic solutions with surface activity will coat ocular, and intraocular structures, and a prosthetic lens during its placement into the eye.

In the present invention, a modified mucopolysaccharide solution is disclosed. The modified mucopolysaccharide solution is used as a biologically active therapeutic infusion, most typically during ophthalmic surgery, such as one ocular and intraocular lens implant procedure. In a specific mode of practicing the present invention, the mucopolysaccharide solution includes a pharmaceutical grade viscoelastic fraction which is selected preferably from hyaluronic acid or an acyl-substituted hyaluronic acid or mixtures of acyl-substituted hyaluronic acid and hyaluronic acid with HPMC and optionally with a biocompatible surfactant; and, hydroxypropylmethylcellulose (HPMC), and absent chondroitin sulfate A, B, or C. The acyl-substituted hyaluronic acids have alky groups with three to twenty carbon atoms. Besides the viscoelastic fraction, the mucopolysaccharide solution usually includes a physiological buffer fraction, conveniently in a predetermined ratio to reach a suitable osmotic level. A solution of between about 250 and about 400 milliosmoles is generally isotonic to ocular tissues. Of course, solutions of higher osmolality will potentially cause a net solute outflow from ocular tissues while those of lower osmolality may permit net solute migration into such tissues. When the physical properties, especially surface activity, of the modified mucopolysaccharide solution are closely controlled, infusion and aspiration at the site of an ophthalmic operation are more manageable and, particularly, the coating at the site of solution contact is enhanced. In order for a solution, gel, or

the like, including mucopolysaccharide solutions of the present invention, (collectively "coating agents") to coat a surface, the surface tension of the coating agent must be lower than the critical surface tension of the surface to be coated. Human corneal endothelium is frequently found to have a critical surface tension of from about 50 to about 56 dynes/cm^2. Thus, in the practice of this invention, a coating agent having a surface tension of less than about 56 dynes/cm^2, and more particularly, less than about 50 dynes/cm^2 is of particular advantage.

In addition to the above, another modified mucopolysaccharide solution is disclosed. The second modified mucopolysaccharide solution is used during ophthalmic surgery for protection of the internal ocular structures, most typically during extraction of a cataractous human lens and the replacement thereof by a prosthetic intraocular lens. In practicing the second embodiment of the invention, the mucopolysaccharide solution includes an optically clear polymeric fraction which is selected preferably from hyaluronic acid; and mixtures of hyaluronic acid, and absent chondroitin sulfate A, chondroitin sulfate B, and chondroitin sulfate C.

In the alternative, modified mucopolysaccharide solution, a second fraction is that of a biologically compatible surfactant. As will be described infra, many free fatty acid and similar surfactants are utilizable in trace quantities to lower the surface tension into the desired range. Besides the viscoelastic and surfactant fractions, mucopolysaccharide

solution includes a physiological buffer fraction in a predetermined ratio between the weight of the viscoelastic fraction (surfactant fraction is not significant in the ratio) and the weight of the buffer fraction. While the physical properties of the modified mucopolysaccharide solution are closely controlled, upon the modified mucopolysaccharide solution being placed in the anterior chamber of the eye during surgery, the surgeon can observe the ocular and intraocular structure through the optically clear solution, and the corneal endothelium is coated and thereby protected from accidental touch by surgical instruments, ocular and intraocular prosthetic devices, and in ocular and intraocular irrigating solutions.

Practitioners in the art frequently attempt to use mucopolysaccharide solutions of particularly high viscosity. However, the use of such high viscosity mucopolysaccharide solutions has been limited by the difficulty encountered in injecting such solutions. Frequently such solutions have not been injectable at forces obtainable in hand held syringes. It has now been discovered that the stress and force required to inject mucopolysaccharide solutions, that is solutions containing macromolecules such as HA and HPMC, decreases as syringe size decreases. Thus syringe injecting a mucopolysaccharide solution of given viscosity, through a needle of given size, e.g. a 23 gauge needle, a 1cc syringe requires substantially less force than a 3 cc syringe and a 3 cc syringe less than a 5 cc syringe. (This generally presumes the standard syringe configurations of inside cross section of 0.16 cm^2 for a

1cc syringe, 0.57 cm^2 for a 3cc and 1.13 cm^2 for a 5 cc syringe.) Fig. 8 provides an exemplary table of such forces. Solutions compared are A, HPMC(H); B, HA(H);, C, HA(L); D, HPMC(H) and HA(L); and, E, HPMC(H) and HA(H). Clearly, the 1cc syringe required less stress at maximum than the wider syringes.

Fig. 9(a) depicts a syringe (10) and plunger (12) with a generally flat lower surface (13) particularly useful in the practice of this invention. The angle θ of the flow path for a viscoelastic through the syringe within the syringe into a cannula (14) is seen to be about 45° or less. Fig. 9(b) depicts an alternative plunger (16) for syringe (10). The lower surface (18) of plunger (16) is shaped to generally conform to angle θ at the bottom of syringe (10). A related embodiment is seen in Fig. 9(c), wherein a syringe (20) and plunger (22) with a generally bulbous lower surface (24). The flow path for a viscoelastic through lower end of the syringe within the syringe into a cannula (14) is seen to be about 45° or less, but sloped and not linear. Unlike the usual regimen associated with administration of medicaments through a syringe, the "dosage" delivered here is determined by observation of the material extruded from the end of the syringe. As such the amount initially in a syringe or remaining in a "dead space" within the syringe and not extrudable by application of pressure on the plunger is of little consequence. This presumes that there is sufficient extrudable capacity of viscoelastic mater to begin with.

An embodiment of this invention is drawn to a method of adhering a contact lens to the surface of the eye, and the apparatus of such method. This is done to permit a medical professional to clearly observe the interior of the eye. That is the contact lens is typically designed for a person other than the subject of the medical procedure to see into the eye. To accomplish this a lens of appropriate optics and conformance to corneal curvature is positioned in on the eye wherein the eye surface is coated with a generally continuous sheet or layer of the viscoelastic solution of this invention. In this application it is particularly important that the viscoelastic solution be generally transparent and bubble free. The arrangement of lens on top of such viscoelastic, on top of the eye permitting a view of the interior of the eye by a person other than the subject is termed "operational-optical connection."

Fig 10(a) (60) and (b) (70) are diagrammatic representations of various embodiments of an apparatus for viewing the interior of the eye (depicted in contact with an eye (50)). Fig. 10(a) represents a side view of contact lens (64) atop a layer of transparent mucopolysaccharide solution of the present invention (62), positioned and optically configured so that an external observer may view internal ophthalmic tissues, surgical instruments, color reactions, or other observable features or phenomena. Fig. 10(b), also having a layer of transparent mucopolysaccharide solution of the present invention (72), replaces the contact lens with the lens (74) of a camera (76). In an additional embodiment, the camera could include a

source of illumination or laser surgical light, or be replaced by or used in combination with a source of illumination or laser light, such as surgical laser light, or even diagnostic light application.

An embodiment of this invention concerns method of hydraulically positioning intra-optic structures or tissues. This is done by the step of applying against such tissues under elevated hydrostatic pressure the modified mucopolysaccharide solution of this invention. In one case, this comprises keeping the lens capsule elevated and away from surgical instruments during surgery such as cataract surgery. In another embodiment this method would include dissecting or elevating tissue such as hyperplastic tissue that has grown over the retina in certain pathologies. The viscoelastic solution is introduced, conveniently, through a needle at the hyperplastic tissue/retina interface. Gradual injection under pressure raises up the hyperplastic tissue. From this raised and free position, the tissue may be removed with out substantial damage to the retina tissue beneath.

METHODS

PURITY CRITERIA

All samples of hyaluronic acid obtained from Chesapeake Biologicals passed the endotoxin Limulus Lysate Assay. The criterion for passing the assay was that, when a sample was dissolved with a physiological buffer to a concentration of 5 mg/ml, less than 0.25 endotoxin units per ml were found.

SURFACE TENSION

Surface tension was measured by a modification of the Wilhelmy Plate method allowing measurement of surface tension of highly viscous polymer solutions. In the Wilhelmy Plate method, the surface tension was measured by immersing a thin platinum blade into the solution to be measured. The blade is slowly withdrawn through its attachment to a surface balance. The surface balance measures the force on the platinum blade, and, as the blade is pulled from the solution, a drop in force is noted. The force is measured in dynes/centimeter. In the modified method that was used in these experiments, surface forces were measured using a sensitive transducer, (manufactured by the Honeywell Co., Minneapolis, Minnesota) attached to a platinum blade and recorder. For surface tensions measurements, about 20 ml of solutions were placed in a petri dish. The dish was placed on a jack-stand and the stand was moved upward until the platinum blade just touched the solution. With this method, surface forces were measured as the platinum blade was pulled into the solution. In the usual Wilhelmy Plate method, the surface forces are measured as the platinum blade is pulled from the solution. For reproducible results, the platinum blade was cleaned and exposed to a flame between usage. All measurements were carried out using freshly prepared solutions at temperatures of 25° ± 1°C.

In some instances, surface tension was measured at 25°C using a tensiometer (Cahn, Model DCA 322, Cerritos CA). Twenty ml of a solution being tested was poured out into a Pyrex™ cover dish and placed on the stage of a tensiometer. All tests were performed at about 17-25°C ("room temperature") using a platform

speed of 104 microns/sec. Data was collected using an IBM-PC™ and DCA-322™ software to obtain surface tension of the receding curve for the material tested.

PREPARATION OF VISCOELASTIC SOLUTIONS

All polymer solutions were diluted to the desired concentration. A buffer solution containing 0.85% sodium chloride, 0.028% disodium hydrogen phosphate dihydrate and 0.004% of sodium hydrogen phosphate hydrate. The dilution varied according to the desired viscosity.

EXAMPLE 1

Sodium hyaluronate + oleic acid

Hyaluronate with an average molecular weight of under 50,000 (Chesapeake Biologicals) was dissolved in buffer solution at room temperature. Potassium oleate was added to achieve a final concentration of 5×10^{-6} mg./ml.

EXAMPLE 2

Acyl-substituted hyaluronate

Acyl-substituted hyaluronate was diluted utilizing phosphate buffer to a final concentration of 30 mg./ml.

EXAMPLE 3

Acyl-substituted hyaluronate + oleic acid + hyaluronate)

Acyl-substituted hyaluronate and hyaluronate together having an average molecular weight of 1×10^6, were diluted in phosphate buffer to achieve a final concentration of 30 mg./ml of sodium hyaluronate and 1 milligram per ml of acyl-substituted hyaluronate. Oleic acid was added to the final solution to achieve a concentration of 1×10^{-6} mg./ml. of potassium oleate.

Example 4

Preparation of acyl-substituted hyaluronic acid

Bioengineered hyaluronic acid from a bacterial source with an average molecular weight of 50,000 is utilized to prepare the substituted hyaluronate. Hyaluronate is dissolved in a dilute sulfuric acid solution and titrated with sulfuric acid to a final pH of 3.0. The solution is heated to 75° C and the acyl anhydride, for example N-butyric, is added to the solution. The solution is constantly stirred. The molar ratio of the two solutes is adjusted to achieve substitution of one hydroxyl group by an acyl group at every 4th to 10th repeating disaccharide unit of hyaluronic acid. The reaction is then allowed to run to completion over an extended period, approximately 24 hours. The solution is then neutralized with 0.1N sodium hydroxide and subsequently dehydrated. The resultant dried solute is used to form subsequent solutions.

Utilizing sodium hyaluronate with molecular weights in the range of 500,000 to 2 x 10^6, an acyl-substituted hyaluronate, and a biologically compatible surfactant, viscoelastic formulations can be made with any desired surface tension, which is compatible with ocular and intraocular use, and which fracture with suction forces in the range of 5 to 400 mm Hg. depending upon the solution properties desired. Unique formulations can be constructed which affect coating of ocular and intraocular structures yet which can be completely aspirated or retarded from aspiration as so desired.

Example 5
Blending Technology

In order to achieve a solution with appropriate fracturing characteristics, two hyaluronic acid species of different average molecular weights were utilized. Both hyaluronic acid fractions were obtained from rooster combs from Chesapeake Biologicals. One fraction had an average molecular weight of 1 x 10^6 Daltons and supplied in a 5 mg/ml concentration. The other fraction consisted of an acid species with an average molecular weight of 500,000 in a concentration of 30 mg/ml From these two species, solutions were constructed based on a volume ratio of one part low molecular weight to two part high molecular weights, hyaluronic acid. At this ratio of molecular weights, the viscous mixture easily fractured when suctioned through a 0.3 mm aspiration cannula when vacuum pressures were applied in the range of 50 to 200 mm Hg. Verification of fracturing characteristics was achieved by direct visualization through a 10X microscope.

Quantification

Viscoelastic solutions meeting the claimed characteristics are directly determinable. Typically a solution of about 4% to about 10% viscoelastic selected from, for example, the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof is useful. Clearly, higher initial percentage concentrations can be employed. Serial dilutions, conveniently in 10x steps are then made, and the viscosity and surface tension repeatedly measured until the desired point is reached. In addition, biocompatible surface active agents may be employed to reduce

surface tension. In mixtures of HPMC and hyaluronic acid, and derivatives thereof, it is useful to note that HPMC contributes little to viscosity while possessing surface activity, while hyaluronic acid and derivatives thereof contribute substantially to viscosity and little to surface activity. In practice a checkerboard dilution and proportion type assay provides a convenient system for determining component proportions within the claimed range. The accompanying graphs, particularly Figs. 6 and 7 will assist in the interpretation of checkerboard results by directing one to the proper parameter by modification of the proper constituent.

Viscosity Measurements

Tested solutions were removed from storage at 4°C and allowed to reach room temperature. After reaching room temperature, 5ml of such solution was injected onto the sample testing plate of a viscometer, Rheometrics Fluids Spectrometer #RFS8400™ (Piscataway, N.J.). The shear rate was linearly increased from 0.3 sec^{-1} to 9.0 sec^{-1} over a period of 9 minutes,
and the viscosity of the solution recorded with a Haake RV 100 plotter. From a plot of viscosity v. shear rate, the viscosity at 0.35 sec^{-1} was extrapolated.

Molecular Weight

Molecular weight may be determined by any of a number of well known techniques such as chromatography and density centrifugation.. A particularly useful method of measuring molecular weight was by the scattered light intensity at an angle of 6-7° using a Chromatic KMX-6™ laser light scattering

device. A detailed description of this method is set forth in "Laser Light Scattering measurements on Vitreous and Rooster Comb Hyaluronic Acids," Int.J.Biol.Macromol., 4:425-9 (1982) incorporated herein by reference. The Optical constant required for molecular weight determinations was obtained using a chromatix KMC-16™ differential refractometer operating at 5°C and at a wavelength of 633nm. The instrument was calibrated by measuring the difference in the refractive index of standard salt solutions with water as the reference material. Once the calibration constant was determined from measurements on salt solutions, the difference in refractive index between each solution and its dialysate was measured at concentrations between 1 and 5mg/ml. The ratio of change in refractive index, Δn, divided by the concentration, c, was plotted against concentration and the value of the refractive index was taken as $\Delta n/c$ extrapolated to zero concentration.

Molecular weight was then obtained by determining the Rayleigh factor, (R_θ) for solutions of unknown concentration, c, between 0.1 and 0.5 mg/ml and plotting Kc/R_θ against concentration (K, the optical constant is calculated using refractive index increment) as shown in Fig. 1, with a calculated molecular weight of 5,560,000. Weight average molecular weight was determined from the reciprocal of Kc/R_θ extrapolated to zero concentration.

Injection Tests

A particular injection load versus time curve is set forth in Fig. 2. The material tested was a high molecular weight HA. Maximum load was determined as the largest load needed to force

the sample from a syringe through a 23 gauge needle. While testing may be accomplished various ways known in the art, HA and HPMC solutions were conveniently tested using a syringe holder fashioned to attach to the compression cell of an Instron Tester Model 1122 (Instron Corp, Sprinfield, N.J.). Force was measured from the load cell and the crosshead was lowered at a rate of 200mm/min. Maximum stress was determined by dividing the peak load by the cross sectional area (interior) of the syringe barrel.

Aspiration Profile

Aspiration behavior was uniformly determined by use of a 23 gauge needle. Test procedure entailed placing a vacuum through the 23 gauge needle onto each sample and determining the fraction of each sample aspirated within 1 minute. The vacuum was increased in 22 mm Hg increments from 0 to 100 mm Hg and the fraction aspirated was determined gravimetrically. From the data represented in Fig. 5, the distinct aspiration characteristic of the viscoelastic solutions of this invention are made clear. The inventive solutions do not aspirate as a bolus at any applicable vacuum level. Of particular importance is the substantially non-sigmoidal curve found upon aspiration of solutions of this invention under the conditions used in compiling the data of Fig. 5. In contrast, HA solutions of comparable viscosity, aspirate as bolus at all but the lowest vacuum levels. In practice, at aspiration vacuum levels designed to provide reasonably prompt removal of less than the total amount of viscoelastic solution, only the inventive solutions will suffice. The shaded area of Fig. 5(a) generally

delimits the particular aspiration characteristic of less than total aspiration of viscoelastic solution of the present invention at vacuum levels above about 50 mm Hg. The aspiration curves at the vacuum levels tested offers reasonable predictability as to those aspiration characteristics that will permit a medical professional to incrementally aspirate a viscoelastic at convenient pressures and over a fairly brief period of time. Solutions with sigmoidal curves aspirate essentially as a bolus and are not suitable. In the 50 to 90 mmHg range under this procedure, and limited to solutions that are substantially non-sigmoidal in aspiration behavior, a slope of from about horizontal up to about 1.5 and more particularly from about horizontal to about 1.0 are preferred, with a slope or aspiration profile of about horizontal to about 0.5 more preferred. It is understood that the slope of an horizontal line is technically an undetermined special case. However, a slightly upward line has a slope of a small positive number. For convenience here, the slope of an horizontal line will be assumed to be zero, and the stated range from horizontal up to slopes of 1 and 1.5, includes horizontal (or even slightly negative slopes). While very high or low vacuum levels or aspiration times are conceivable, they are less useful, except in unique circumstances. Unduly high aspiration vacuum levels pose a danger to ocular structures. Unduly long aspiration times, generally in excess of 2 or 3 minutes, unduly prolong surgical procedures.

Again referencing Fig. 7, Aspiration profile is presented in Z axis, forming, as plotted against viscosity and surface tension a theoretical cube of the claimed viscoelastic solution. Points A, B, C and D are at a viscosity of 100,000 mPa·s. Points E, F, G, and H are at a viscosity of 10,000 mPa·s. Points A, D, E, and H are at Aspiration Profile of O. Points B, C, F, and G are at Aspiration Profile points of 1.5. Points A, B, E, and F are at Surface Tension of 40 dynes/cm. Points D, C, H and G are at Surface Tension of 65 dynes/cm. Point I represents Occucoat and point II represents Healon, each beyond the enclosed area.

With the techniques and examples described above, the novel and unobvious modified mucopolysaccharide solutions of this invention are presented in the claims which follow. Minor changes and adjustments may be made by those skilled in the art without departing from the spirit of this invention.

TABLE 1. *Products and solutions used or tested for use in ophthalmic surgery*

Product	Manufacturer	Polymer	Concentration	Molecular weight
Healon	Pharmacia	HA	10	~4,000,000
Amvisc	Med-Chem Products	HA	~10	~2,500,000
IaL	Fidia	HA	20	~500,000
Viscoat	Cilco	HA+	30	~500,000
		CS	40	~30,000
CS 50%	—	CS	500	~20,000
HPMC 2%	—	HPMC	20	~100,000
Collagen	3M	Collagen	20	320,000→gel

HA—hyaluronan, CS—Chondroitin sulphate,
HPMC—hydroxypropylmethylcellulose.

WHAT IS CLAIMED;

Claim 1. The modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

Claim 2. A modified mucopolysaccharide solution as described in Claim 1 having a surface tension of less than about 56 dynes/cm^2.

Claim 3. A modified mucopolysaccharide solution as described in Claim 2 having a surface tension of less than about 50 dynes/cm^2.

Claim 4. A modified mucopolysaccharide solution as described in Claim 1 wherein said viscoelastic fraction has an average molecular weight of at least 50,000.

Claim 5. A modified mucopolysaccharide solution as described in Claim 1 wherein said viscoelastic fraction is an acyl-substitute hyaluronic acid having acyl groups thereof with three to twenty carbon atoms.

Claim 6. A modified mucopolysaccharide solution as described in Claim 1 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount sufficient to produce said surface tension.

Claim 7. A modified mucopolysaccharide solution as described in Claim 6 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml.

Claim 8. The modified mucopolysaccharide of Claim 7 wherein said surfactant fraction of a biocompatible component is a free fatty acid.

Claim 9. A modified mucopolysaccharide solution as described in Claim 4 wherein said viscoelastic fraction is a mixture of said acyl-substituted hyaluronic acid and hyaluronic acid.

Claim 10. A modified mucopolysaccharide solution as described in Claim 9 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount sufficient to produce said surface tension.

Claim 11. A modified mucopolysaccharide solution as described in Claim 10 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml.

Claim 12. The modified mucopolysaccharide solution of Claim 1 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 13. The solution of Claim 12 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 14. A modified mucopolysaccharide solution as described in Claim 12 further including the surfactant is oleic acid.

Claim 15. The modified mucopolysaccharide of Claim 12 wherein said surfactant fraction of a biocompatible component is a free fatty acid.

Claim 16. A modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with

three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

Claim 17. A modified mucopolysaccharide solution as described in Claim 16 having a surface tension of less than about 56 dynes/cm^2.

Claim 18. A modified mucopolysaccharide solution as described in Claim 17 having a surface tension of less than about 50 dynes/cm^2.

Claim 19. A modified mucopolysaccharide solution as described in Claim 16 wherein said polymeric fraction is hyaluronic acid.

Claim 20. The modified mucopolysaccharide solution of Claim 16 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 21. The solution of Claim 20 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 22. A pharmaceutically acceptable modified mucopolysaccharide solution absent chondroitin sulfate having a surface tension of between 40 and 65 dynes/cm^2; and,

a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C.

Claim 23. A modified mucopolysaccharide solution as described in Claim 22 having a surface tension of less than about 56 dynes/cm^2.

Claim 24. A modified mucopolysaccharide solution as described in Claim 23 having a surface tension of less than about 50 dynes/cm^2.

Claim 25. The solution of claim 22 wherein said mucopolysaccharide is a surface active mucopolysaccharide.

Claim 26. The solution of claim 25 further comprising a biological surfactant selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants.

Claim 27. The solution of Claim 22 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 28. The solution of Claim 27 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 29. The solution of Claim 22 wherein said mucopolysaccharide has an average molecular weight of at least 50,000.

Claim 30. The solution of Claim 29 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 31. The solution of Claim 30 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 32. A method of protecting internal ocular structures during ocular surgery and retarding aspiration of material from the ocular surgery site by the step of:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction with a surface tension of between 40 and 65 dynes/cm^2; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C.

Claim 33. The method of Claim 32 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 cm^2 in cross section or less.

Claim 34. The method of Claim 32 wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm^2.

Claim 35. The method of claim 34 wherein the modified mucopolysaccharide solution has a surface tension of less than about 50 dynes/cm^2.

Claim 36. The method of claim 32 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 37. The method of claim 36 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 38. A method of protecting internal ocular structures during ocular surgery by providing a viscoelastic solution that coats ocular structures at a surgical site such that aspiration of the viscoelastic solution is retarded, said method being:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution absent chondroitin sulfate and having a surface tension of between 40 and 65 dynes/cm^2; and,

a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C.

Claim 39. The method of Claim 38 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 mm in cross section or less.

Claim 40. A modified mucopolysaccharide solution as described in Claim 38 having a surface tension of less than about 56 dynes/cm^2.

Claim 41. A modified mucopolysaccharide solution as described in Claim 40 having a surface tension of less than about 50 dynes/cm^2.

Claim 42. The method of claim 41 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 43. The method of claim 42 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 44. A method of protection of internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

intraocularly introducing a modified mucopolysaccharide solution during ophthalmic surgery wherein said solution comprises

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

Claim 45. The method of Claim 44 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 mm in cross section or less.

Claim 46. The method of claim 44 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 47. The method of claim 46 wherein said solution, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 48. A modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 $dynes/cm^2$; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

Claim 49. A modified mucopolysaccharide solution as described in Claim 48 having a surface tension of less than about 56 dynes/cm^2.

Claim 50. A modified mucopolysaccharide solution as described in Claim 47 having a surface tension of less than about 50 dynes/cm^2.

Claim 51. A modified mucopolysaccharide solution for use as a biologically active therapeutic infusion as delimited by the shaded area of Fig. 7.

Claim 52. A method of adhering a contact lens to the surface of the eye in operational-optical connection with said eye, by the step of interposing between said lens and said eye surface an adhering amount of substantially transparent modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

Claim 53. A method of hydraulically positioning intra-optic structures or tissues by the step of applying against such tissues under elevated hydrostatic pressure modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C.

Claim 54. The method of Claim 53 wherein the tissue is hyperplastic tissue, positioned over the retina and said applying is performed by injecting said solution between said tissue and the retina, said positioning resulting in raising the tissue of of the retina.

FIG. 1

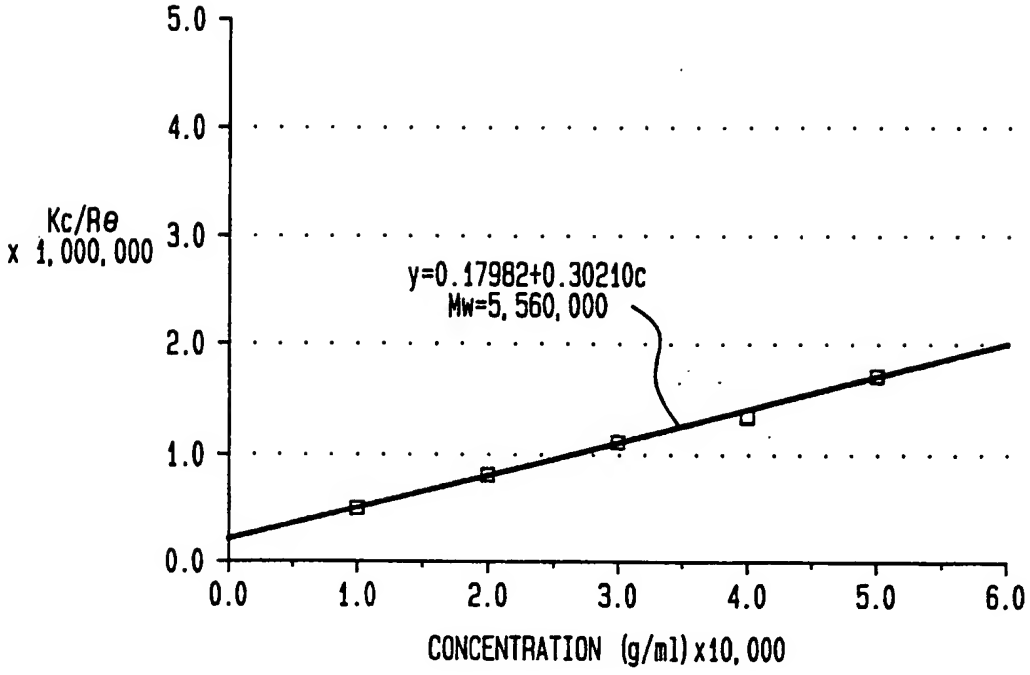

Kc/Rθ
x 1,000,000
5.0
4.0
3.0
2.0
1.0
0.0
y=0.17982+0.30210c
Mw=5,560,000
0.0
1.0
2.0
3.0
4.0
5.0
6.0
CONCENTRATION (g/ml) x10,000

FIG. 2

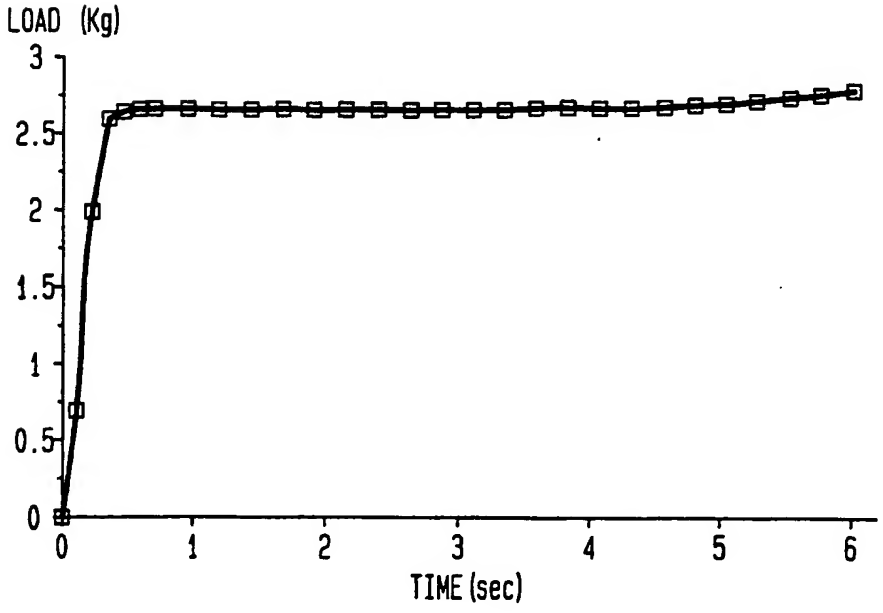

LOAD (Kg)
3
2.5
2
1.5
1
0.5
0
0
1
2
3
4
5
6
TIME (sec)

FIG. 3

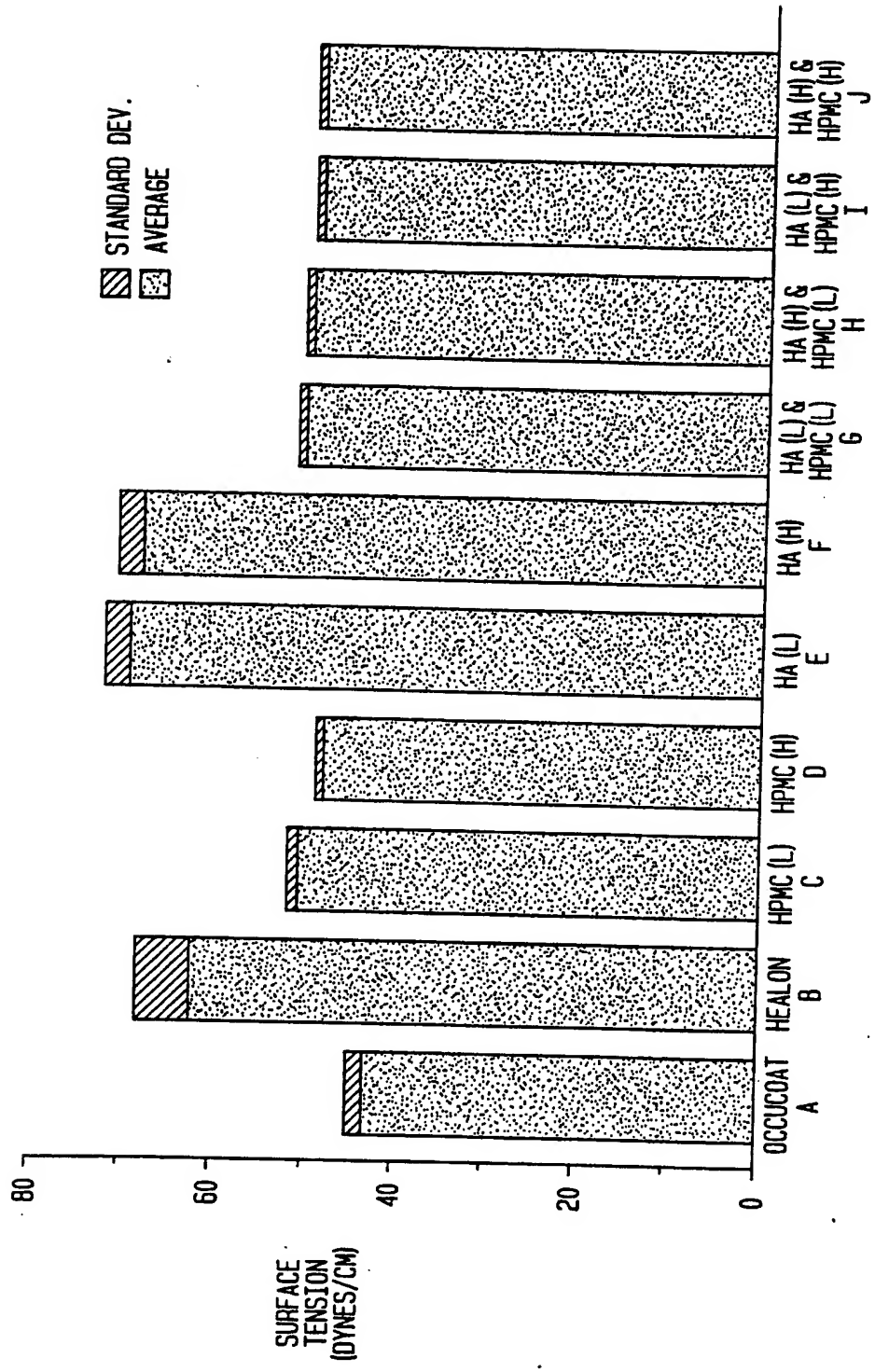

STANDARD DEV.
AVERAGE
SURFACE TENSION (DYNES/CM)
0
20
40
60
80
OCCUCOAT A
HEALON B
HPMC (L) C
HPMC (H) D
HA (L) E
HA (H) F
HA (L) & HPMC (L) G
HA (H) & HPMC (L) H
HA (L) & HPMC (H) I
HA (H) & HPMC (H) J

FIG. 4

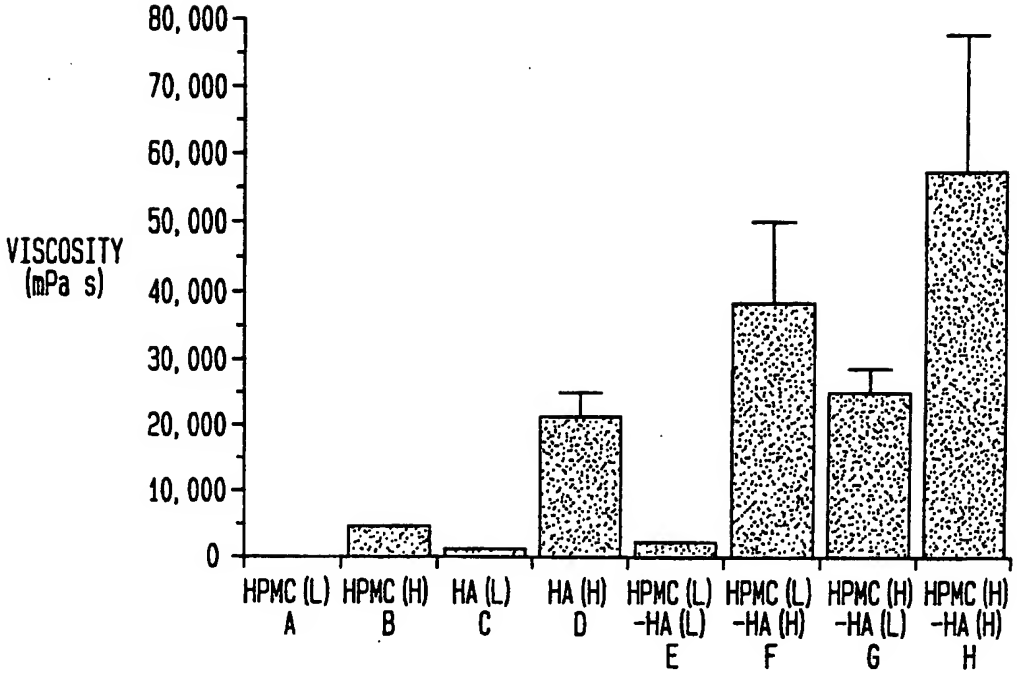

VISCOSITY
(mPa s)
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
HPMC (L) A
HPMC (H) B
HA (L) C
HA (H) D
HPMC (L) -HA (L) E
HPMC (L) -HA (H) F
HPMC (H) -HA (L) G
HPMC (H) -HA (H) H

FIG. 5

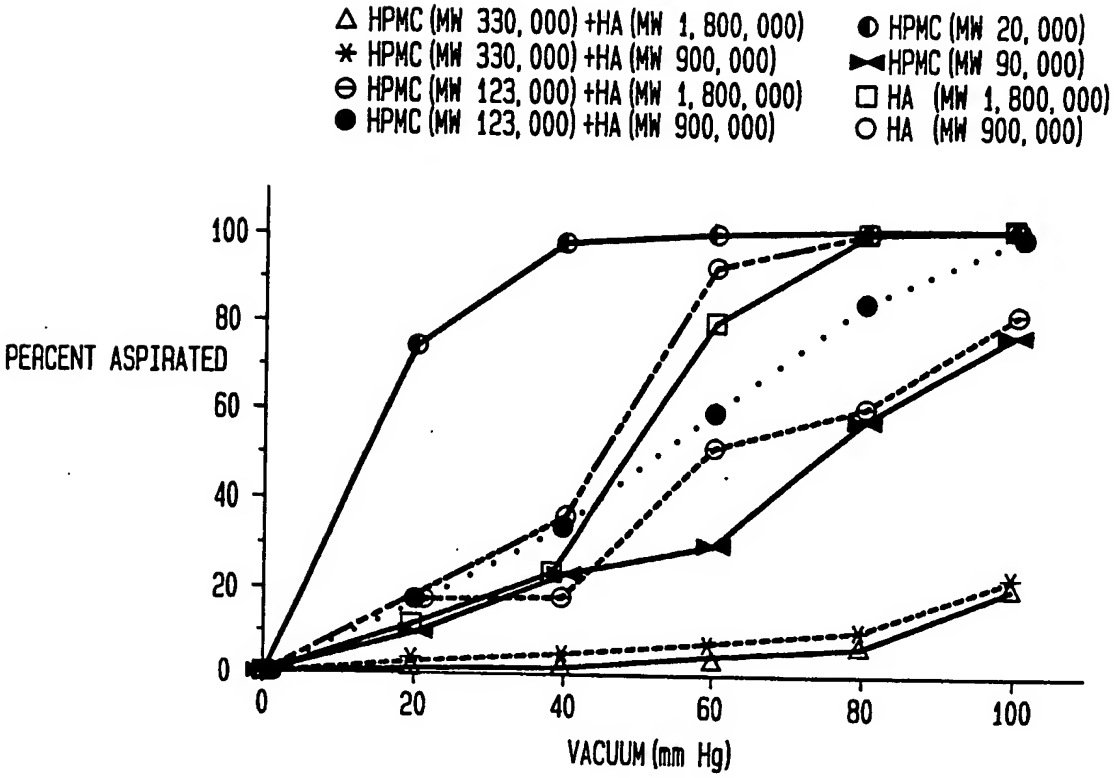

△ HPMC (MW 330, 000) +HA (MW 1, 800, 000)
✳ HPMC (MW 330, 000) +HA (MW 900, 000)
⊖ HPMC (MW 123, 000) +HA (MW 1, 800, 000)
● HPMC (MW 123, 000) +HA (MW 900, 000)
◐ HPMC (MW 20, 000)
⋈ HPMC (MW 90, 000)
□ HA (MW 1, 800, 000)
○ HA (MW 900, 000)
PERCENT ASPIRATED
0
20
40
60
80
100
VACUUM (mm Hg)

FIG. 5A

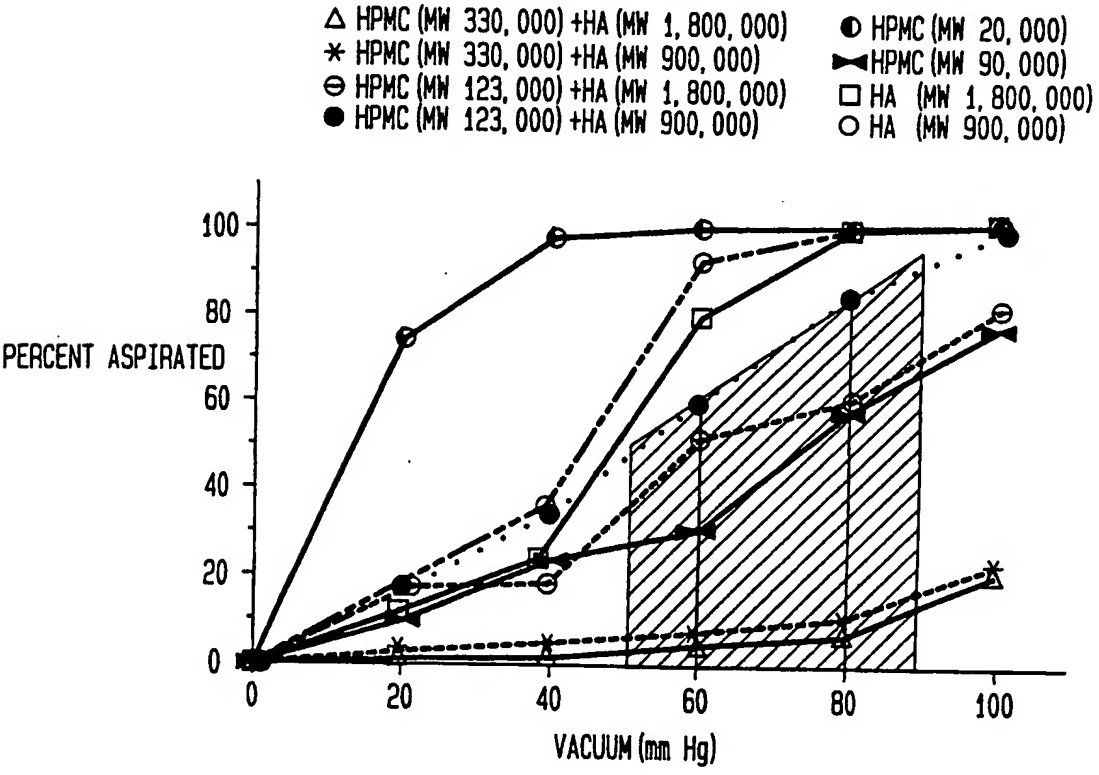

△ HPMC (MW 330, 000) +HA (MW 1, 800, 000)
✳ HPMC (MW 330, 000) +HA (MW 900, 000)
⊖ HPMC (MW 123, 000) +HA (MW 1, 800, 000)
● HPMC (MW 123, 000) +HA (MW 900, 000)
◐ HPMC (MW 20, 000)
⋈ HPMC (MW 90, 000)
□ HA (MW 1, 800, 000)
○ HA (MW 900, 000)
PERCENT ASPIRATED
0
20
40
60
80
100
VACUUM (mm Hg)

FIG. 6

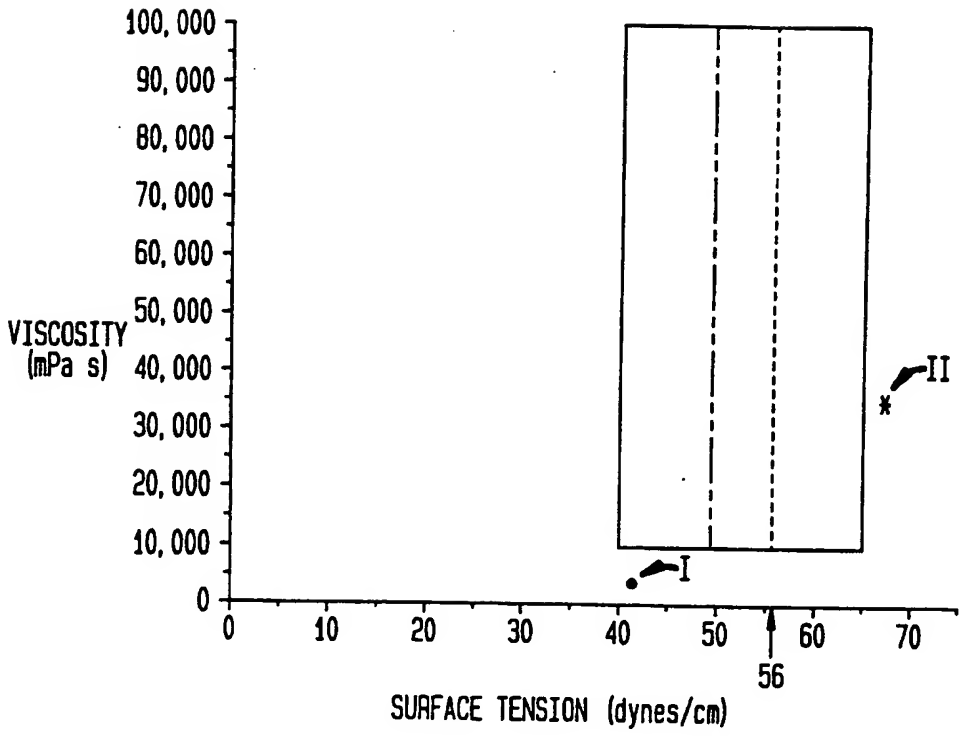

100,000
90,000
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
VISCOSITY (mPa s)
0
10
20
30
40
50
60
70
56
I
II
SURFACE TENSION (dynes/cm)

FIG. 7

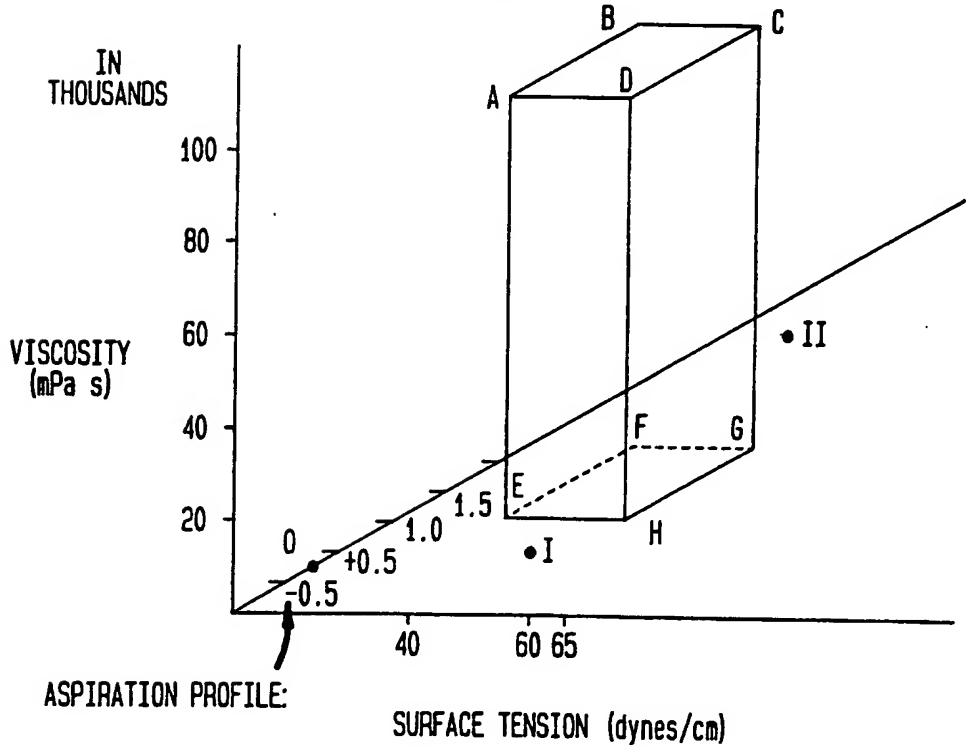

IN THOUSANDS
100
80
60
40
20
VISCOSITY (mPa s)
A
B
C
D
E
F
G
H
I
II
0
+0.5
-0.5
1.0
1.5
40
60 65
ASPIRATION PROFILE:
SURFACE TENSION (dynes/cm)

FIG. 8

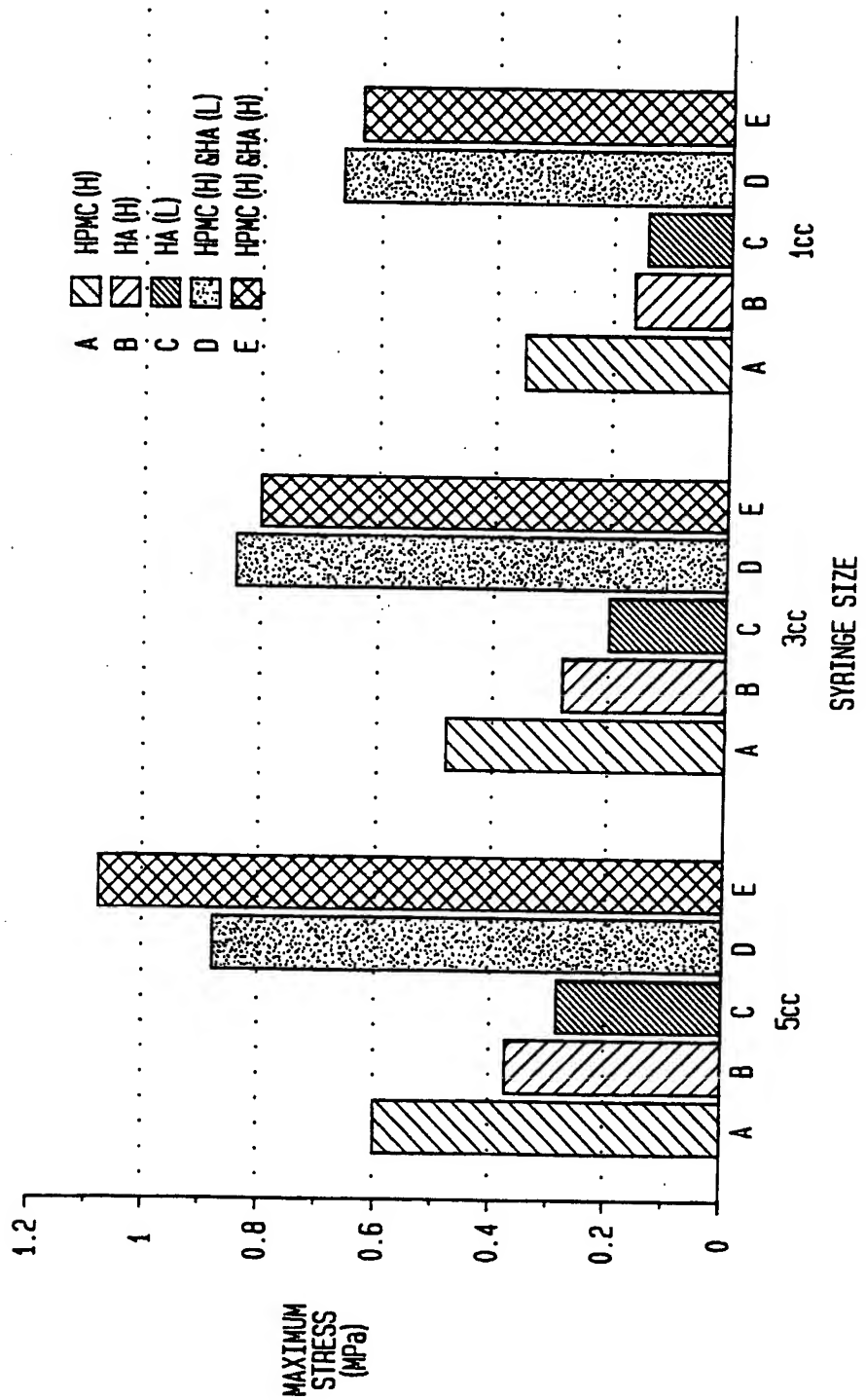

HPMC (H)
HA (H)
HA (L)
HPMC (H) &HA (L)
HPMC (H) &HA (H)
A
B
C
D
E
MAXIMUM STRESS (MPa)
0
0.2
0.4
0.6
0.8
1
1.2
5cc
3cc
1cc
SYRINGE SIZE

FIG. 9A

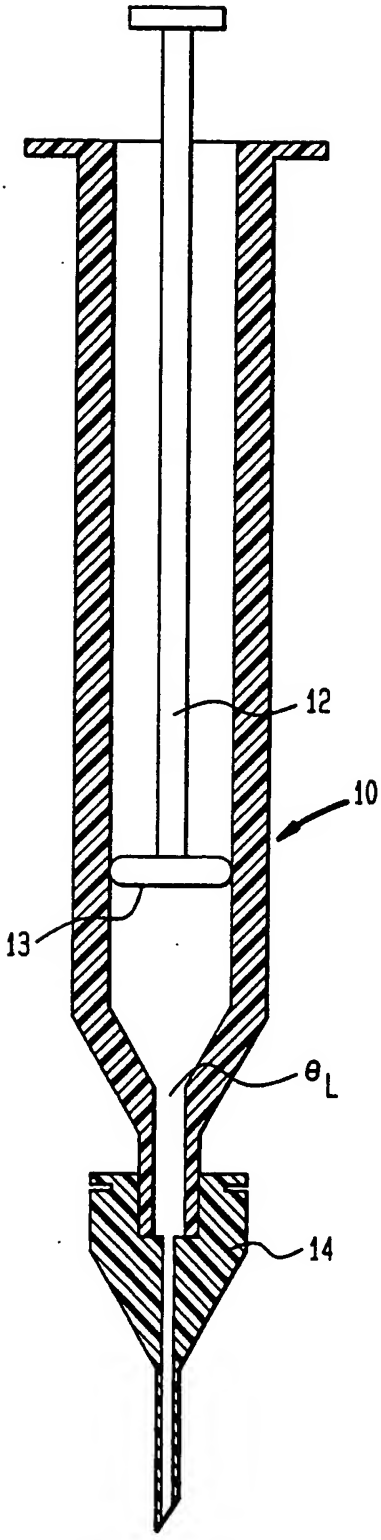


FIG. 9B

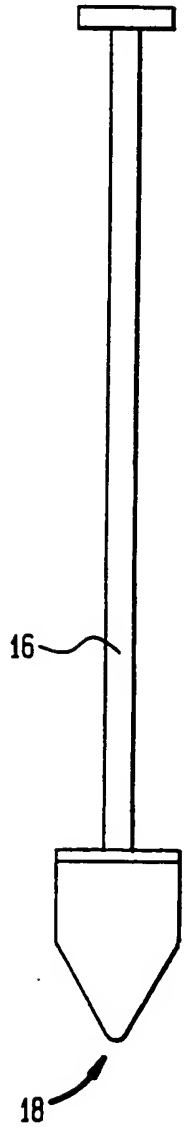


FIG. 9C

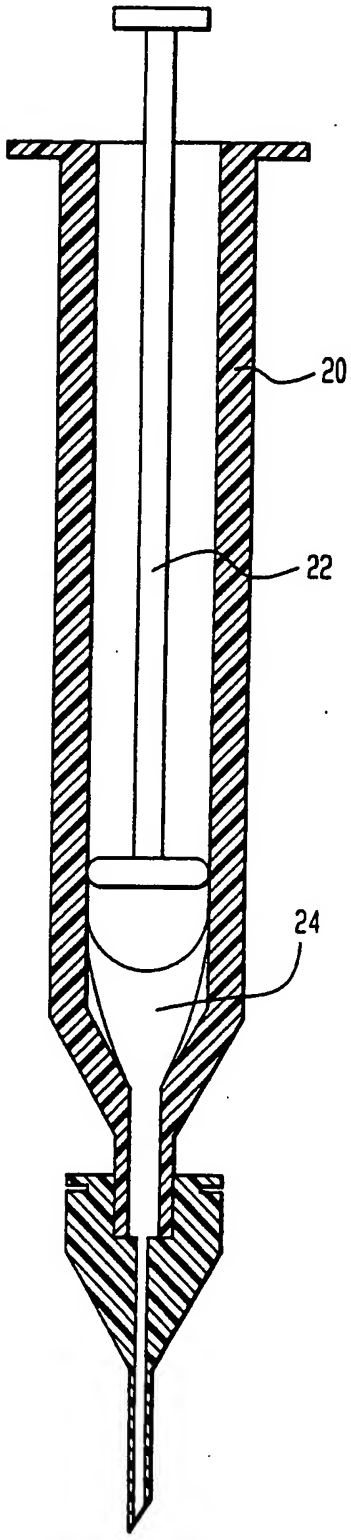


FIG. 10A

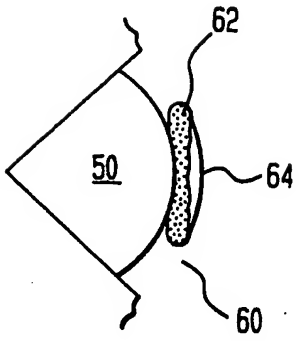
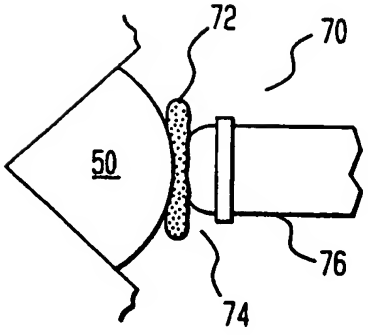


FIG. 10B



INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/US94/10175

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/70; A61F 13/20; G02C 7/02
US CL :514/54; 351/177; 604/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/54; 351/177; 604/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,713,375 (LINDSTROM ET AL.) 15 December 1987, col. 1, lines 22-37 and col. 2, lines 1-3.	1-51
Y	US, A, 4,767,463 (BRODE ET AL.) 30 August 1988, col. 12, lines 17-42.	6-8, 10-11, 26
Y	US, A 4,851,521 (DELLA VALLE ET AL.) 25 July 1989, col. 1, lines 48-68, col. 3, lines 3-59.	1-51
Y	Survey of Ophthalmology, Volume 34, No. 4, issued January-February 1990, Liesegang et al, "Viscoelastic Substances in Ophthalmology", pages 268-293, especially pages 269-272.	1-51

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 DECEMBER 1994	DEC 28 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ELLI PESELEV Telephone No. (703) 308-0196

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